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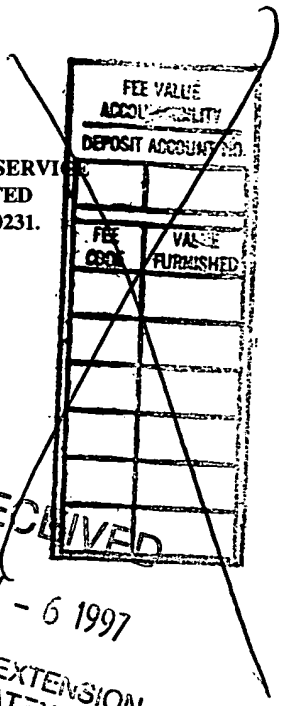

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PATENT EXTENSION
A/C PATENTS

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A/C PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,452,808
Issued: June 5, 1984
To: Gregory Gallagher, Jr.
For: 4-Aminoalkyl-2(3H)-Indolones

Assistant Commissioner of Patents
Box Patent Extension
Washington, D.C. 20231

RE: Deposit Account No. 19-2570
SmithKline Beecham Corporation
U.S. Patent No. 4,452,808

Sir:

Transmitted herewith is an application for extension of patent term under 35 U.S.C. §156 with regard to U.S. Patent No. 4,452,808. Two copies are submitted as duplicate originals.

Please charge our Deposit Account No. 19-2570 in the amount of $1,120.00. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Account No. 19-2570. A duplicate copy of this sheet is enclosed.

Respectfully submitted,
SMITHKLINE BEECHAM CORPORATION

Stephen Venetianer
Attorney for Applicant
Registration No. 25,659

SMITHKLINE BEECHAM CORPORATION
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-5040
Facsimile (610)270-5090

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,452,808

Issued: June 5, 1984

To: Gregory Gallagher, Jr.

For: 4-Aminoalkyl-2(3H)-Indolones

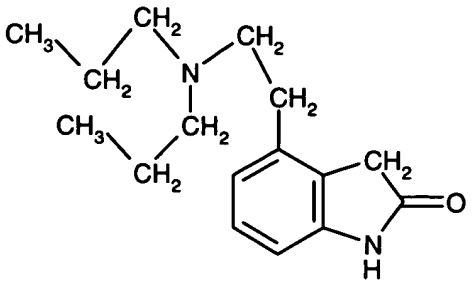
APPLICATION FOR EXTENSION
OF PATENT TERM UNDER 35 U.S.C. §156

Assistant Commissioner of Patents
Box Patent Extension
Washington, D.C. 20231

Sir:

The Applicant, SmithKline Beecham Corporation, a Pennsylvania corporation, represents that it is the Assignee of the entire right, title and interest in and to United States Patent No. 4,452,808 granted to SmithKline Beckman Corporation on June 5, 1984, for 4-Aminoalkyl-2(3H)-Indolones by virtue of an assignment recorded on December 7, 1982 at Reel 4075, Frame 116, and by virtue of a name change from SmithKline Beckman Corporation to SmithKline Beecham Corporation filed on July 26, 1989 filed pursuant to Article VIII of the Business Corporation Law of Pennsylvania. A copy of the assignment is attached as Attachment A. A copy of the Certification reflecting the name change and a copy of the Certificate of Amendment to that affect is attached as Attachment B and C. The Applicant hereby requests an extension of term of U.S. Patent No. 4,452,808 under 35 U.S.C. §156. The following information as required by 37 C.F.R. §1.740 is set forth below:

(1) The approved product is "REQUIP" (Ropinirole) which is 4-[2-(Dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one monohydrochloride and has the following structure:



(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act section 505 (21 U.S.C. §355).

(3) The approved product, "REQUIP" (Ropinirole) received permission for commercial marketing or use under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355) on September 19, 1997.

(4) The only active ingredient in the approved product "REQUIP" (Ropinirole) is 4-[2-(Dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one monohydrochloride. The active ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act or any other Acts.

(5) This application for extension of patent term under 35 U.S.C. §156 is being submitted within the sixty day period permitted for submission under 37 C.F.R. §1.1720(f), the last day for said submission being November 18, 1997.

(6) The complete identification of the patent for which an extension is being sought is as follows:

Inventor: Gregory Gallagher, Jr.

Patent Number: 4,452,808

Issue Date: June 5, 1984

Date of Expiration: December 7, 2002

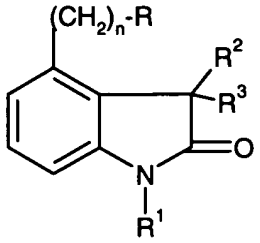
(7) A copy of the patent for which an extension is being sought is attached herewith as "Attachment D".

(8) A copy of the Certificate of Correction for U.S. Patent No. 4,452,808 is attached hereto as Attachment E. A copy of the receipts for the payment of maintenance fees are attached as "Attachment F", "Attachment G", and "Attachment H".

(9) U.S. Patent 4,452,808 claims the approved product as identified in paragraph one hereinabove. More specifically, the approved product is claimed in claims one, two, three, four, five, eight, nine, and ten of U.S. patent 4,452,808 as follows:

Claim one reads:

1. A compound of the structural formula:



in which:

n is 1-3,

R is amino, C_{1-6}lower alkylamino, di-(C_{1-6}-lower alkyl)amino, allylamino, diallylamino, N-(C_{1-6}-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethyl amino or di-(4-hydroxyphenethyl)amino, and

R^1, R^2 and R^3 are, each, hydrogen or C_{1-4}-lower alkyl; or a pharmaceutically acceptable, acid addition salt thereof.

The approved product "REQUIP" (Ropinirole) is claimed when n is two, R^1, R^2 and R^3 are hydrogen, R is di(C_{1-6}-lower akyl)amino and the compound is a pharmaceutically acceptable acid addition salt thereof.

2. The compound of claim 1 in which R^1, R^2 and R^3 are hydrogen, n is 2 and R is amino, di-n-propylamino, n-propyl-n-butylamino or 4-hydroxyphenethylamino.

The approved product "REQUIP" (Ropinirole) is claimed in claim two when R is di-n-propylamino.

3. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

The approved product "REQUIP" (Ropinirole) is the hydrochloride salt of the compound claimed in claim 3.

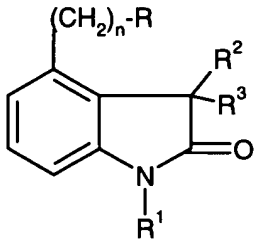
4. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone as the free base.

The approved product "REQUIP" (Ropinirole) is the hydrochloride salt of the free base claimed in claim four.

5. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride.

The approved product "REQUIP" (Ropinirole) is claimed specifically is claim five.

8. A pharmaceutical composition having D_2 receptor agonist activity comprising a nontoxic, agonist quantity of a compound of the structural formula:



in which:

n is 1 to 3

R is amino, C_{1-6}lower alkylamino, di-(C_{1-6}-lower alkyl)amino, allylamino, diallylamino, N-(C_{1-6}-lower alkyl)-N-allylamino, benzylamino, bibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethyl amino or di-(4-hydroxyphenethyl)amino, and

R^1, R^2 and R^3 are, each, hydrogen or C_{1-4}-lower alkyl; or a pharmaceutically acceptable, acid addition salt thereof, in dosage unit form, combined with a pharmaceutical carrier.

The approved product "REQUIP" (Ropinirole) is claimed in claim 8 when n is two, R^1, R^2 and R^3 are hydrogen and R is di-(C_{1-6}-lower alkyl)amino and the compound is a pharmaceutically acceptable acid addition salt.

9. The composition of claim 8 in which the D_2-agonist compound is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

The approved product "REQUIP" (Ropinirole) is a pharmaceutically acceptable acid addition salt of the composition of claim nine.

10. The composition of claim 8 in which the D_2-agonist compound is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride.

The approved product "REQUIP" (Ropinirole) is claimed in Claim 10.

(10) The relevant dates and information pursuant to 35 U.S.C. 156 (g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) The Effective date of the investigational new drug ("IND") application for "REQUIP" (Ropinirole) was July 10, 1988, IND Number 31,712;

(b) New drug application ("NDA") for "REQUIP" (Ropinirole) was initially submitted on January 2, 1996 as NDA 20-658;

(c) NDA 20-658 for "REQUIP" (Ropinirole) was approved on September 19, 1997.

(11) A brief description of the activities undertaken by the applicant during the applicable regulatory review period with respect to "REQUIP" (Ropinirole) and the significant dates applicable to such activities is attached herewith as "Attachment I".

(12) Applicant is of the opinion that U.S. Patent No. 4,452,808 is eligible for extension under 35 USC §156 because it satisfies all the requirements for such extension as follows:

(a) 35 U.S.C. §156(a)

U.S. Patent No. 4,452,808 claims a product;

(b) 35 U.S.C. §156(a)(1)

The term of U.S. Patent No. 4,452,808 has not expired before submission of this application for extension;

(c) 35 U.S.C 156 (a)(2)

The term of U.S. Patent No. 4,452,808 has never been extended;

(d) 35 U.S.C. §156 (a)(3)

The application for extension is submitted by the owner of record of U.S. Patent No. 4,452,808 in accordance with the requirements of 35 U.S.C. §156(d) and the rules of the U.S. Patent and Trademark Office;

(e) 35 U.S.C. §156 (a)(4)

The product, "REQUIP" (Ropinirole), has been subject to a regulatory review period before its commercial marketing or use;

(f) 35 U.S.C. §156(a)(5)(A)

The permission for the commercial marketing or use of the product, "REQUIP" (Ropinirole), after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355), under which such regulatory review period occurred; and

(g) 35 U.S.C. §156(c)(4)

No other patent has been extended for the same regulatory review period for the product "REQUIP" (Ropinirole).

(13) The length of extension of the patent term of U.S. Patent No. 4,452,808 claimed by applicant is five years, the maximum possible under 35 U.S.C. §156(g)(6)(A). The length of the extension was determined pursuant to 37 C.F.R. §1.775 as follows:

(a) The regulatory review period under 35 U.S.C. §156 (g)(1)(B) was from July 10, 1988 until September 19, 1997 which is 3,356 days. which is the sum of (1) and (2) below.

(i) The period of review, under 35 U.S.C. §156(g)(1)(B)(i), the "Testing Period", was from July 10, 1988 (effective date of IND) until January 2, 1996 (NDA submission date), which is 2,731 days.

(ii) The period of review, under 35 U.S.C. §156(g)(1)(B)(ii), the "Application Period", was from January 2, 1996 (NDA submission date) until September 19, 1997 (NDA approval date), which is 625 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub-paragraph (13)(a) above (3,356 days) less

(i) the number of days in the regulatory review period which were on or before the date on which the patent issued (June 5, 1984) which is zero (0) days [3,356 remaining], and

(ii) The number of days during which applicant did not act with due diligence which is zero (0) days [3,356 remaining], and

(iii) One-half the number of days determined in sub-paragraph (13)(a)(i) after substracting (b)(i) and (ii), or 1,366 days, which leaves 1,991 days;

(c) The number of days as determined in sub-paragraph (13)(b) (1,991 days) when added to the original term of the patent would result in the date, March 8, 2008;

(d) Fourteen (14) years when added to the date of NDA approval (September 19, 1997) would result in the date, September 19, 2011;

(e) The earlier date as determined in sub-paragraphs (13)(c) and (13)(d) is March 8, 2008;

(f) Since the original patent was issued before September 24, 1984, and no request for exemption was filed until after September 24, 1984, five (5) years when added to the original expiration date of the patent (December 2, 2002) would result in the date, December 2, 2007; and

(g) The earlier date as determined in sub-paragraph (13)(e) and (13)(f) is December 2, 2007.

Therefore, the length of extension of patent term claimed by Applicant is five (5) years, which is the period of time needed to extend the original expiration of term until December 2, 2007.

(14) Applicant and the undersigned acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination to be made relative to this application for extension.

(15) The prescribed fee of One Thousand One Hundred and Twenty Dollars ($1,120.00) for receiving and acting upon this application of extension is to be charged to applicant's Deposit Account 1902570 as authorized in the accompanying letter, which is submitted in duplicate.

(16) Please direct all inquiries and correspondence relating to this application for patent term extension to:

Stephen Venetianer, Esquire
SmithKline Beecham Corporation
709 Swedeland Road
P.O. Box 1539
King of Prussia, PA 19406-0939

(17) Attached hereto is a Declaration signed on behalf of SmithKline Beecham Corporation which meets the criteria set forth in 37 CFR §1.740(b).

Respectfully submitted,

SMITHKLINE BEECHAM CORPORATION

Stephen Venetianer
Attorney for Applicant
Registration No. 25,659

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156 including its attachments and supporting papers is being submitted as duplicate originals.

Date: November 6, 1997

Stephen Venetianer

N:\SV\PATEXREQ.DOC

ATTACHMENT A

FEBRUARY 8, 1983

TO: WILLIAM H. EDGERTON
P. O. BOX 7929
PHILADELPHIA, PA 19101

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 GALLAGHER, GREGORY JR. DOC DATE: 12/06/82

RECORDATION DATE: 12/07/82 NUMBER OF PAGES 001 REEL/FRAME 4075/0116

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 SMITHKLINE BECKMAN CORPORATION, ONE FRANKLIN PLAZA, PHILADELPHIA, PA 19103 A CORP OF PA

SERIAL NUMBER 6-447564 FILING DATE 12/07/82
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: 4-AMINOALKYL-2(3H)-INDOLONES

INVENTOR: 001 GALLAGHER,

5.10.

SKB 14136

ASSIGNMENT

WHEREAS I, GREGORY GALLAGHER, JR. of 1130 Hollow Road, Collegeville, Pennsylvania 19426, have made an invention entitled:

"4-AMINOALKYL-2(3H)-INDOLONES"

for which on December 6, 1982, I executed an application for Letters Patent of the United States:

NOW, THEREFORE, in consideration of One Dollar ($1.00) and other valuable consideration paid to me by SMITHKLINE BECKMAN CORPORATION, a corporation organized under the laws of the State of Pennsylvania and having its principal place of business at One Franklin Plaza, Philadelphia, Pennsylvania, 19103, the receipt of which is hereby acknowledged, and intending to be legally bound, I do hereby assign unto the said SMITHKLINE BECKMAN CORPORATION, its successors and assigns, the entire right, title and interest in and to the said invention, said executed application, any division, continuation and continuation-in-part of said application, and all Letters Patent of the United States and all foreign countries to be obtained therefor;

I further assign to the said SMITHKLINE BECKMAN CORPORATION the right, optionally in its own name or in the names of its related companies, to apply for, obtain and maintain in all countries foreign to the United States, patent and/or Utility Model applications for said invention, including the full right to claim for any such application the benefits of any priority rights based on said executed United States application;

And I agree to execute further instruments (including divisional, continuation, continuation-in-part or reissue applications or other instruments) proper to effectuate the premises, this agreement to be binding upon my heirs, executors and administrators;

And I request the Commissioner of Patents and Trademarks of the United States, and any official of any country or countries foreign to the United States whose duty it is to issue patents on applications as aforesaid, to issue Letters Patent in accordance herewith.

Signed at Philadelphia, Pennsylvania

Date: December 6, 1982

PATENT & TRADEMARK OFFICE

DEC - 7 1982

Gregory Gallagher Jr.

GREGORY GALLAGHER, JR.

State of Pennsylvania
County of Philadelphia

COMMISSIONER OF PATENTS AND TRADEMARKS

Before me, a Notary Public, personally appeared Gregory Gallagher, Jr. known to me to be the person who executed the foregoing assignment and acknowledged it to be his act and deed.

Witness my hand and seal this 6th day of December, 1982.

Gertrude S. Halbherr

GERTRUDE S. HALBHERR
Notary Public, Phila., Phila. Co.
My Commission Expires March 15, 1986

REEL 4075 FRAME 116

ATTACHMENT I

REQUIP®

Chronology of Significant Activities

IND 31,712 Submissions

Date (Serial Number)	Action	Description
June 10, 1988 (000)	Initial IND	
July 19, 1988 (001)	Amendment to IND	Information Amendment: Pharmacology/Toxicology reports
August 18, 1988 (002)	Response to FDA Request for Information	Response to questions regarding chemistry of the drug substance
October 3, 1988 (003)	Amendment to IND	New protocol A05 and Pharmacology/Toxicology reports
December 2, 1988 (004)	IND Safety Report	Initial safety report
March 17, 1989 (005)	Amendment to IND	Letter to investigator sent as a result of safety report
March 20, 1989 (006)	Response to FDA Request for Information	Response to questions regarding chemistry and manufacture of the drug substance and drug product and preclinical sections of the original IND
June 12, 1989 (007)	Amendment to IND	Updated specifications for tablets
July 28, 1989 (008)	Response to FDA Request for Information	Additional information regarding the impurity profile of Route B material
September 26, 1989 (009)	IND Safety Report	Initial safety report
October 26, 1989 (010)	Amendment to IND	Pharmacology/Toxicology reports
November 14, 1989 (011)	IND Safety Report	Follow-up safety report
November 16, 1989 (012)	Annual report	
January 12, 1990 (013)	Response to FDA Request for Information	Confirmation of meeting with FDA for January 24, 1990
February 2, 1990 (014)	Letter to FDA	Minutes of January 24, 1990 meeting with FDA

Date (Serial Number)	Action	Description
April 10, 1990 (015)	IND Safety Report	Initial safety report
April 11, 1990 (016)	Amendment to IND	Revised Chemistry, Manufacturing and Controls information relevant to Route B material
August 1, 1990 (017)	Amendment to IND	Change of corporate name
August 6, 1990 (018)	IND Safety Report	Follow-up safety report
September 21, 1990 (019)	Annual Report	
October 5, 1990 (020)	Amendment to IND	Pharmacology/Toxicology reports
October 22, 1990 (021)	Amendment to IND	New protocol C7106
December 7, 1990 (022)	IND Safety Report	Initial safety report
December 20, 1990 (023)	Response to FDA Request for Information	Information regarding the 1 year monkey study
January 18, 1991 (024)	IND Safety Report	Follow-up safety report
February 14, 1991 (025)	IND Safety Report	Follow-up safety report
February 28, 1991 (026)	Amendment to IND	Pharmacology/Toxicology reports
March 8, 1991 (027)	General Correspondence	Request that the clinical hold be lifted
June 21, 1991 (028)	IND Safety Report	Initial safety report
June 21, 1991 (029)	Response to FDA Request for Information	Information regarding the 1 year monkey study
June 24, 1991 (030)	IND Safety Report	Follow-up safety report
June 25, 1991 (031)	IND Safety Report	Initial safety report
June 26, 1991 (032)	IND Safety Report	Follow-up safety report
July 10, 1991 (033)	IND Safety Report	Follow-up to a written report
July 12, 1991 (034)	IND Safety Report	Follow-up to a written report (revision)
July 19, 1991 (035)	Amendment to IND	Revised protocol, new investigators and container labels for protocol C7106
August 12, 1991 (036)	IND Safety Report	Follow-up to safety report
August 12 1991 (037)	Amendment to IND	New investigators for protocol C7106

Date (Serial Number)	Action	Description
August 13, 1991 (038)	Amendment to IND	Pharmacology/Toxicology reports
August 16, 1991 (039)	Annual report	
August 16, 1991 (040)	IND Safety Report	Follow-up to a written report (revision)
September 5, 1991 (041)	Amendment to IND	Revised drug product manufacturing directions; updated drug substance and drug product stability data
September 12, 1991 (042)	Amendment to IND	New investigators for protocol C7106
November 25, 1991 (043)	General correspondence	New safety monitors
November 25, 1991 (044)	Amendment to IND	Pharmacology/Toxicology and Clinical reports
November 26, 1991 (045)	Amendment to IND	New investigators for protocol C7106; new protocols C7107 and C7107A
December 6, 1991 (046)	Amendment to IND	Details of new route D synthesis
February 24, 1992 (047)	Amendment to IND	Pharmacology/Toxicology and Clinical reports
February 28, 1992 (048)	Request for Guidance	Review of Phase III plans
March 23, 1992 (049)	Amendment to IND	New investigators for protocols C7107 and C7107A
June 2, 1992 (050)	Amendment to IND	New investigators for protocols C7107 and C7107A
June 18, 1992 (051)	Amendment to IND	Pharmacology/Toxicology and Clinical reports
July 7, 1992 (052)	IND Safety Report	Follow-up to a written report (revision)
August 20, 1992 (053)	Amendment to IND	Change in protocol 044 and 054
August 27, 1992 (054)	Amendment to IND	New investigators for protocol 044 and 054; updated Chemistry, Manufacturing and Controls information

Date (Serial Number)	Action	Description
August 31, 1992 (055)	Amendment to IND	New protocol 090
September 8, 1992 (056)	Annual report	
October 7, 1992 (057)	IND Safety Report	Initial preclinical (toxicology) written report
October 22, 1992 (058)	IND Safety Report	Follow-up to a written report
November 10, 1992 (059)	IND Safety Report	Initial safety report
November 20, 1992 (060)	Amendment to IND	New investigators for protocols 044 and 054
December 17, 1992 (061)	IND Safety Report	Follow-up to a written report
January 25, 1993 (062)	IND Safety Report	Follow-up to a written report
February 5, 1993 (063)	IND Safety Report	Follow-up to a written report
February 11, 1993 (064)	IND Safety Report	Follow-up to a written report
March 5, 1993 (065)	IND Safety Report	Follow-up to a written report
March 8, 1993 (066)	Amendment to IND	New protocol, new investigators and container labels for protocol 055
March 11, 1993 (067)	Amendment to IND	New investigators for protocols: 040, 041, 092, 044 and 054; container labels for protocol C7107(041)
March 22, 1993 (068)	Amendment to IND	Pharmacology/Toxicology and Clinical reports
April 12, 1993 (069)	Amendment to IND	New protocol, new investigators and container labels for protocol 051
April 20, 1993 (070)	Request for End of Phase 2 Meeting	
May 25, 1993 (071)	Amendment to IND	Pharmacology/Toxicology reports
July 8, 1993 (072)	IND Safety Report	Initial safety report
July 14, 1993 (073)	IND Safety Report	Initial safety report
July 22, 1993 (074)	SB Minutes of the End of Phase 2 Meeting	

Date (Serial Number)	Action	Description
August 6, 1993 (075)	Amendment to IND	Change in protocol 092 and new/revised investigator information for protocols 041, 044, 051, 054 and 055
October 8, 1993 (076)	Amendment to IND	Pharmacology/Toxicology reports
September 10, 1993 (077)	IND Safety Report	Initial safety report
September 14, 1993 (078)	Annual report	
September 27, 1993 (079)	IND Safety Report	Follow-up safety report
October 8, 1993 (080)	Amendment to IND	Pharmacology/Toxicology reports
October 26, 1993 (081)	General correspondence	SB Minutes of FDA/SB telephone conference
December 1, 1993 (082)	General correspondence	New safety monitor
December 30, 1993 (083)	Amendment to IND	New/revised investigator information for protocols 044, 051, 054, 055 and 092
January 24, 1994 (084)	IND Safety Report	Initial safety report
February 7, 1994 (085)	IND Safety Report	Initial safety report
February 16, 1994 (086)	IND Safety Report	Initial safety report
February 21, 1994 (087)	IND Safety Report	Initial safety report
February 25, 1994 (088)	Amendment to IND	Change in protocol and new investigator for protocol 090
March 15, 1994 (089)	General correspondence	Request waiver from *in vivo* bioequivalence trial
April 6, 1994 (090)	IND Safety Report	Initial safety report
April 12, 1994 (091)	Amendment to IND	New/revised investigator information for protocols 051, 054, 055 and 090
April 22, 1994 (092)	Amendment to IND	Modified synthetic processes and analytical data

Date (Serial Number)	Action	Description
April 27, 1994 (093)	Amendment to IND	New investigator information for protocol 090
April 29, 1994 (094)	Amendment to IND	Chemistry, Manufacturing and Controls information on five strengths of white tablets (0.25, 0.5, 1, 2 and 5 mg)
May 10, 1994 (095)	IND Safety Report	Initial safety report
May 24, 1994 (096)	IND Safety Report	Follow-up safety report
June 9, 1994 (097)	Response to FDA Request for Information	Information requested at end of Phase 2 meeting
June 29, 1994 (098)	Request for Guidance	Analysis of efficacy data for phase 3 studies
June 30, 1994 (099)	Amendment to IND	New investigator and new safety monitor information for protocol 090
July 1, 1994 (100)	IND Safety Report	Initial safety report
July 12, 1994 (101)	IND Safety Report	Follow-up safety report
July 15, 1994 (102)	General Correspondence	New safety monitor
July 29, 1994 (103)	Amendment to IND	Pharmacology/Toxicology and Clinical reports
August 12, 1994 (104)	IND Safety Report	Initial safety report
August 15, 1994 (105)	Amendment to IND	New/revised investigator information for protocols 041, 054, 055 and 090
August 19, 1994 (106)	IND Safety Report	Initial safety report
August 25, 1994 (107)	IND Safety Report	Initial safety report
September 2, 1994 (108)	Annual Report	
October 12, 1994 (109)	IND Safety Report	Initial safety report
October 21, 1994 (110)	IND Safety Report	Follow-up safety report
October 28, 1994 (111)	IND Safety Report	Initial and follow-up safety reports
November 11, 1994 (112)	IND Safety Report	Initial and follow-up safety reports
November 29, 1994 (113)	IND Safety Report	Initial and follow-up safety reports
December 5, 1994 (114)	IND Safety Report	Follow-up safety report

Date (Serial Number)	Action	Description
December 8, 1994 (115)	IND Safety Report	Follow-up safety report
December 16, 1994 (116)	IND Safety Report	Follow-up safety report
December 20, 1994 (117)	IND Safety Report	Follow-up safety report
December 21, 1994 (118)	IND Safety Report	Initial safety report
December 22, 1994 (119)	Request for Pre-NDA Meeting	Briefing document for Pre-NDA meeting
December 23, 1994 (120)	IND Safety Report	Follow-up safety report
January 19, 1995 (121)	Response to FDA Request for Information	Addendum to Pre-NDA briefing document
January 23, 1995 (122)	IND Safety Report	Follow-up safety report
January 26, 1995 (123)	IND Safety Report	Follow-up safety report
February 1, 1995 (124)	General Correspondence	New safety monitor
February 9, 1995 (125)	IND Safety Report	Follow-up safety report
February 9, 1995 (126)	Response to FDA request for Information	Response to questions in FDA letter of 28 November 1994
February 20, 1995 (127)	Response to FDA Request for Information	Addendum to Pre-NDA briefing document
February 9, 1995 (128)	IND Safety Report	Follow-up safety report (copy of serial #125 to correct error in serial #)
March 1, 1995 (129)	IND Safety Report	Initial safety report
March 29, 1995 (130)	IND Safety Report	Follow-up safety report
April 3, 1995 (131)	Amendment to IND	Pharmacology/Toxicology reports
April 5, 1995 (132)	IND Safety Report	Follow-up safety report
April 6, 1995 (133)	General Correspondence	SB minutes of the pre-NDA meeting
April 11, 1995 (134)	General Correspondence	Toxicology Interaction Studies
April 14, 1995 (135)	Letter to FDA	Briefing document for scheduled meeting of 25 April 1995
April 18, 1995 (136)	IND Safety Report	Follow-up safety report

Date (Serial Number)	Action	Description
April 18, 1995 (137)	Response to FDA Request for Information	Biopharmaceutics data
May 11, 1995 (138)	Amendment to IND	New/revised investigator information for protocols 051, 055 and 090
May 22, 1995 (139)	General Correspondence	SB minutes of meeting of FDA and SB statisticians
June 5, 1995 (140)	General Correspondence	SB minutes of pre-NDA meeting - CMC
June 13, 1995 (141)	IND Safety Report	Follow-up safety report
July 26, 1995 (142)	IND Safety Report	Initial safety report
August 3, 1995 (143)	IND Safety Report	Follow-up safety report
August 3, 1995 (144)	General Correspondence	Trademark
August 7, 1995 (145)	IND Safety Report	Follow-up safety report
September 14, 1995 (146)	Annual Report	
September 12, 1995 (147)	General Correspondence	Correction of error in volume/page numbers
October 23, 1995 (148)	IND Safety Report	Initial safety report
October 27, 1995 (149)	IND Safety Report	Follow-up safety report

REQUIP®

Chronology of Significant Activities

IND 31,712 Submissions: Post NDA Submission (December 29, 1995)

Date (Serial Number)	Action	Description
January 3, 1996 (150)	IND Safety Report	Initial safety report
January 18, 1996 (151)	IND Safety Report	Initial safety report
January 31, 1996 (152)	IND Safety Report	Follow-up safety report
February 8, 1996 (153)	IND Safety Report	Follow-up safety report
February 15, 1996 (154)	IND Safety Report	Follow-up safety report
March 1, 1996 (155)	IND Safety Report	Initial safety report
March 12, 1996 (156)	IND Safety Report	Follow-up safety report
April 5, 1996 (157)	IND Safety Report	Follow-up safety report
July 29, 1996 (158)	IND Safety Report	Initial safety report
August 9, 1996 (159)	IND Safety Report	Follow-up safety report
August 26, 1996 (160)	IND Safety Report	Follow-up safety report
September 3, 1996 (161)	IND Safety Report	Follow-up safety report
September 13, 1996 (162)	Annual Report	
September 10, 1996 (163)	IND Safety Report	Follow-up safety report
October 23, 1996 (164)	IND Safety Report	Follow-up safety report
November 13, 1996 (165)	IND Safety Report	Initial safety report
November 18, 1996 (166)	IND Safety Report and Amendment to IND	Initial safety report and investigator letter
February 14, 1997 (167)	IND Safety Report	Initial safety report
February 27, 1997 (168)	IND Safety Report and Amendment to IND	Initial safety report and investigator letter
March 6, 1997 (169)	IND Safety Report	Initial and follow-up safety report
March 19, 1997 (170)	IND Safety Report	Initial safety report
April 24, 1997 (171)	IND Safety Report and Amendment to IND	Initial safety report and investigator letter
April 30, 1997 (172)	IND Safety Report	Follow-up safety report
May 15, 1997 (173)	IND Safety Report	Follow-up safety report
May 30, 1997 (174)	IND Safety Report	Initial safety report
June 30, 1997 (175)	IND Safety Report	Follow-up safety report

Date (Serial Number)	Action	Description
July 8, 1997 (176)	Amendment to IND	Pharmacology/Toxicology reports
July 10, 1997 (177)	IND Safety Report and Amendment to IND	Initial safety report and investigator letter
July 15, 1997 (178)	Amendment to IND	New protocol, new investigators and labels for protocol 125
July 18, 1997 (179)	IND Safety Report	Initial safety report
August 15, 1997 (180)	IND Safety Report	Initial and follow-up safety report
August 21, 1997 (181)	IND Safety Report	Initial and follow-up safety report and investigator letter
August 27, 1997 (182)	General Correspondence	New safety monitor
September 4, 1997 (183)	IND Safety Report	Follow-up safety report
September 4, 1997 (184)	Annual Report	
September 17, 1997 (185)	Amendment to IND	Correction of CMC information provided in Serial # 178
September 22, 1997 (186)	IND Safety Report	Follow-up safety report

REQUIP®
Chronology of Significant Activities
NDA 20-658 Submissions

Date (Serial Number)	Action	Description
December 29, 1995; received by FDA January 2, 1996	NDA	
March 6, 1996 (1)	Response to FDA Request for Information	Attachments 1-5 of clinical study 038 for FDA statistical reviewer
March 8, 1996 (2)	Response to FDA Request for Information	Pharmacokinetics synopses in WordPerfect and raw data
March 20, 1996 (3)	Response to FDA Request for Information	Carcinogenicity SAS datasets
March 22, 1996 (4)	General Correspondence	Review status
March 28, 1996 (5)	General Correspondence	CANDA Revisions
April 4, 1997 (6)	Response to FDA Request for Information	SAS datasets for clinical studies 054 and 032
April 11, 1996	Response to FDA Request for Information	Sent to FDA Compliance with regard to location of specific investigator information and compliance statements
April 17, 1996 (7)	Response to FDA Request for Information	SAS datasets for clinical study 044
April 19, 1996 (8)	Response to FDA Request for Information	SAS datasets for clinical study 040
April 30, 1996 (9)	Response to FDA Request for Information	Information requested by compliance regarding FDA site audits
July 11, 1996 (10)	Response to FDA Request for Information	Case report forms for syncope patients
July 16, 1996 (11)	Response to FDA Request for Information	Unannotated labeling in WordPerfect
October 3, 1996 (12)	Correspondence	Safety update
November 8, 1996 (13)	Response to Request	Safety update
January 8, 1997 (14)	Correspondence	Response to approvable letter
January 23, 1997 (15)	Correspondence	Briefing document
February 13, 1997 (16)	Correspondence	SB minutes of 31 January 1997 telephone conference
March 28, 1997 (17)	Response to the Approvable Letter	Safety update

Date (Serial Number)	Action	Description
April 9, 1997 (18)	Revision to Serial # 17	
May 6, 1997 (19)	Response to Request for Information	Eye lesions observed in carcinogenicity studies
June 20, 1997 (20)	Amendment to NDA	Degradation product
August 19, 1997 (21)	Final Printed Labeling	
August 19, 1997 (22)	Amendment to NDA	Dissolution testing methodology and specifications
August 25, 1997 (23)	General Correspondence	Draft labeling

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,452,808

Issued: June 5, 1984

To: Gregory Gallagher, Jr.

For: 4-AMINOALKYL-2(3H)-INDOLONES

Assistant Commissioner of Patents
Box Patent Extension
Washington, DC 20231

DECLARATION

Sir:

The undersigned, Attorney for SmithKline Beecham Corporation, which is the applicant for extension of patent term under 35 U.S.C. §156 with respect to U.S. Patent No. 4,452,808 hereby declares that:

(1) That he is an attorney authorized to practice before the Patent and Trademark Office and that he has general authority from the owner to act on behalf of the owner in patent matters.

(2) He has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. §156 and the guidelines for extension of patent term under 37 C.F.R. §1.740.

(3) He believes the patent is subject to extension pursuant to 35 U.S.C. §156 and the guidelines for extension of patent term under 37 C.F.R. §1.710.

(4) He believes an extension of the length claimed is fully justified under 35 U.S.C. §156 and the applicable regulations; and

(5) He believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. §156 and the guidelines for extension of patent term under 37 C.F.R. §1.720.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Date: November 6, 1997

Stephen Venetianer
Registration No. 25,659

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N:\SV\PATDEREQ.DOC

DSCB-221-(9-71)

ATTACHMENT B

Commonwealth of Pennsylvania

September 7, 1990

Department of State

TO ALL TO WHOM THESE PRESENTS SHALL COME, GREETING:

Pennsylvania, ss:

I DO HEREBY CERTIFY, That from an examination of the indices and corporate records of this department, it appears that 'Smithkline Beckman Corporation', a Pennsylvania corporation, incorporated June 29, 1929, changed its corporate name to "SMITHKLINE BEECHAM CORPORATION", by virtue of Articles of Amendment herein filed July 26, 1989, pursuant to the provisions of Article VIII of the Business Corporation Law.

I DO FURTHER CERTIFY, That "SMITHKLINE BEECHAM CORPORATION" remains a presently subsisting corporation as of the date hereof.

IN TESTIMONY WHEREOF, I have hereunto set my hand and caused the Great Seal of the Commonwealth to be affixed, the day and year above written.

Christopher A. Lewis

Secretary of the Commonwealth clk

ATTACHMENT C

8953 184

Commonwealth of Pennsylvania

Department of State

To All to Whom These Presents Shall Come, Greeting:

Whereas, *In and by Article VIII of the Business Corporation Law, approved the fifth day of May, Anno Domini one thousand nine hundred and thirty-three, P. L. 364, as amended, the Department of State is authorized and required to issue a*

CERTIFICATE OF AMENDMENT

evidencing the amendment of the Articles of Incorporation of a business corporation organized under or subject to the provisions of that Law, and

Whereas, *The stipulations and conditions of that Law pertaining to the amendment of Articles of Incorporation have been fully complied with by*

SMITHKLINE BECKMAN CORPORATION
name changed to
SMITHKLINE BEECHAM CORPORATION

Therefore, Know Ye, *That subject to the Constitution of this Commonwealth and under the authority of the Business Corporation Law, I do by these presents, which I have caused to be sealed with the Great Seal of the Commonwealth, extend the rights and powers of the corporation named above, in accordance with the terms and provisions of the Articles of Amendment presented by it to the Department of State, with full power and authority to use and enjoy such rights and powers, subject to all the provisions and restrictions of the Business Corporation Law and all other applicable laws of this Commonwealth.*

Given, *under my Hand and the Great Seal of the Commonwealth, at the City of Harrisburg, this* 26th *day of* July *in the year of our Lord one thousand nine hundred and* eighty-nine *and of the Commonwealth the two hundred fourteenth.*

Secretary of the Commonwealth

DSCB-21 (7-78)

CAS

ATTACHMENT D

United States Patent [19]

Gallagher, Jr.

[11] **4,452,808**

[45] **Jun. 5, 1984**

[54] **4-AMINOALKYL-2(3H)-INDOLONES**

[75] Inventor: **Gregory Gallagher, Jr.**, Collegeville, Pa.

[73] Assignee: **Smithkline Beckman Corporation**, Philadelphia, Pa.

[21] Appl. No.: **447,564**

[22] Filed: **Dec. 7, 1982**

[51] **Int. Cl.**³ **C07D 209/32**; A61K 31/40

[52] **U.S. Cl.** **424/274**; 548/486

[58] **Field of Search** 548/486; 424/274

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,573,310	3/1971	Van Dyke	548/486
4,317,944	2/1982	Huffman et al.	

FOREIGN PATENT DOCUMENTS

895875	3/1972	Canada	548/486

Primary Examiner—Donald G. Daus
Assistant Examiner—A. Hendricks
Attorney, Agent, or Firm—William H. Edgerton; Richard D. Foggio; Alan D. Lourie

[57] **ABSTRACT**

A series of new chemical compounds which are 4-aminoalkyl-2(3H)-indolones has been demonstrated to be D_2-agonists useful for treating hypertension. A representative compound of the series is 4-di-n-propylaminoethyl-2(3H)-indolone.

12 Claims, No Drawings

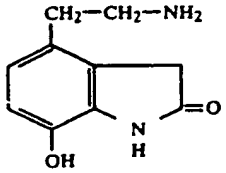
4-AMINOALKYL-2(3H)-INDOLONES

This invention relates to certain novel 4-aminoalkyl-2(3H)-indolones as well as to anti-hypertensive compositions and methods which use them.

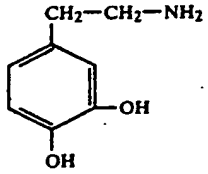
BACKGROUND OF THE INVENTION

4-Aminoalkyl-7-hydroxy-2(3H)-indolones are described in U.S. Pat. No. 4,314,944 to have a beneficial effect on abnormal conditions of the cardiovascular system. More specifically, such compounds are said to have a vasodilatation effect on the kidney which is similar to that of dopamine, thereby inducing antihypertensive activity due to a dopaminergic mechanism.

The basic structure of the prior art compounds is similar to that of the well known cardiovascular agent they mimic, dopamine:



U.S. Pat. No. 4,314,944



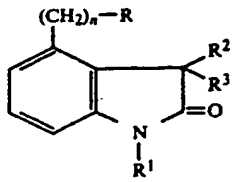
Dopamine

One skilled in the structure function art will appreciate that the 7-hydroxy group of the compounds of the prior art is necessary for them to resemble the structure of dopamine. Without this key group, the resulting compounds would not be expected to have cardiovascular activity.

DESCRIPTION OF THE INVENTION

The indolone compounds of this invention have beneficial cardiovascular activity despite the lack of the supposedly essential 7-hydroxy group. In addition to not having a catechol or catechol-mimicking structure, these indolones may not be subject to tachyphylaxis and are better absorbed orally when compared with the prior art compounds based on preliminary pharmacological tests with the preferred species of this invention.

The compounds are illustrated by the following structural formula:



I

in which:

R is amino, lower alkylamino, di-lower alkylamino, allylamino, diallylamino, N-lower alkyl-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethylamino or di-(4-hydroxyphenethylamino);

R^1, R^2 or R^3 are, each, hydrogen or lower alkyl; and

n is 1-3.

A subgeneric group of this invention comprises the compounds of formula I in which:

R is amino, di-n-propylamino, n-propyl-n-butylamino or 4-hydroxyphenethylamino;

R^1, R^2 or R^3 are hydrogen; and

$(CH_2)_n$ is ethylene ($-CH_2-CH_2-$).

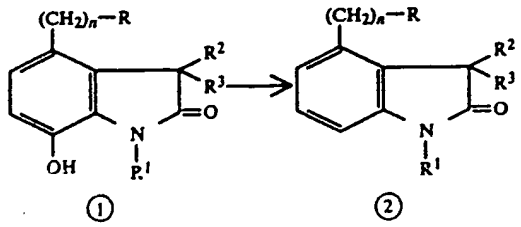
A preferred species of this invention is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or one of its pharmaceutically acceptable, acid addition salts.

The term "lower alkyl" used herein and in the claims is meant, for convenience, to include branched and straight chain groups of from 1-6 carbons, preferably n-propyl, for each alkyl in R and from 1-4 carbons, preferably methyl, for each of R^1, R^2 and R^3. R^1, R^2 and R^3 are preferably, for ease of preparation, all the same.

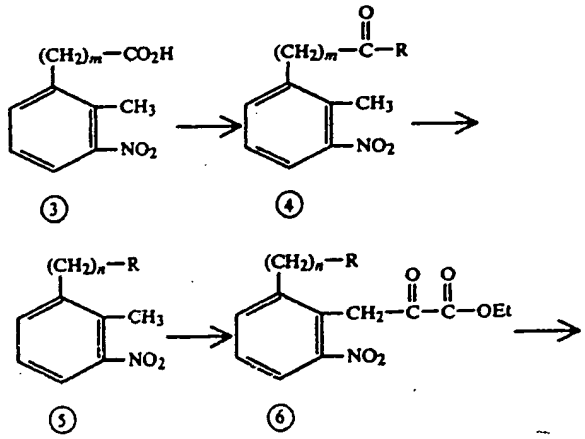
The pharmaceutically acceptable acid addition salts having the utility of the free bases of formula I are part of this invention. These are prepared by methods well known to the art and are formed with both inorganic or organic acids, for example: maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methane sulfonic, ethane disulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids. The hydrohalic and, especially, methane sulfonic acid salts are conveniently used.

The compounds of this invention are prepared by the following reaction sequences:

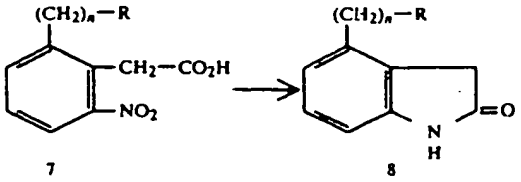
Scheme A



Scheme B



-continued



In the reaction sequences of Schemes A and B above, n, R, R^1, R^2 and R^3 are as described for formula I; m is n−1. In some cases, such as where R is a primary or secondary amino, a protective group may be present, as described in more detail below.

In addition to the reaction sequences noted above, the compounds of this invention are prepared by the reactions which are described in U.S. Pat. No. 4,314,944, using, of course, known deshydroxy or desmethoxy starting materials. In preparing the present 7-unsubstituted indolones by this route, the ring closure to form the isatin ring at column 2 of that patent can proceed to give two isomeric products which must then be separated to yield the indolones of this invention.

In Scheme A, the corresponding 7-hydroxy indolone starting material (1) is de-hydroxylated by reacting it with at least a stoichiometric quantity of a reactive 5-halo-1-phenyl-1H-tetrazole in the presence of an acid binding agent, such as an alkali metal carbonate, in a suitable inert solvent, such as aqueous acetone, dimethylformamide or dimethylacetamide. The reaction is carried out at room temperature until substantially complete. From one to two days may be used. If desired, the reaction may be carried out in shorter time by operating at a higher temperature, for example, up to 75°.

The resulting new intermediate, a 4-(aminoalkyl)-7-(1-phenyl-1H-tetrazazol-5-yloxy)-2(3H)-indolone, is subjected to hydrogenation to split the tetrazole-oxyindolone link. Conveniently, catalytic hydrogenation, for example using a noble metal catalyst at moderate pressures of hydrogen and some heat, such as palladium-on-charcoal at 50° for 20 hours under 55 p.s.i., is used.

When R is a reactive amino, the starting material (1) is used in the form of an acid addition salt or an otherwise amino protected derivative. If a hydrogenation labile protective group is present on compound 1, it is also split during the reduction.

The reactions of Sequence B involve the insertion of the aminoalkyl side chain into the phenyl ring (1→7) followed by ring closure of the o-carboxymethyl-m-nitro intermediate (7). The ring closure is carried out by reduction of the intermediate, for example, using catalytic hydrogenation over a noble metal, preferably palladium, catalyst in a suitable solvent, for example, a lower alcohol, dilute hydrochloric acid or glacial acetic acid, at moderate pressures of hydrogen and at a temperature chosen from the range of room temperature to 60°. The reaction proceeds quickly to completion. The nitro group of compound 7 is reduced first, followed by ring closure.

As noted above, this reaction sequence is adaptable to prepare the compounds having a reactive aminoalkyl side chain by protecting an amine or another reactive group with a standard protecting means such as forming a maleimide, tert. boc or phthalimide derivative, which is removed, by standard reactions, after ring closure. The phthalimido protective group, for example, is split using reaction with hydrazine hydrate. A benzyloxy is split by using catalytic hydrogenation; a tert.-boc, using mild acid.

The alkylated products of this invention are, alternatively, or, in certain instances, preferentially prepared by alkylation of the parent amino compounds of formula I in which R is amino or a secondary amino. For example, the N-alkylated products, formula I when R is a secondary or tertiary amino, are conveniently prepared by reductive alkylation using, for example, the aldehyde in one or two molar equivalent quantities under reduction conditions, such as under catalytic hydrogenation conditions over a palladium or platinum catalyst or such as using formaldehyde-formic acid when R is dimethylamino.

N-Alkylation, such as using an allyl or benzyl halide in the presence of an acid binding agent, can be used under standard mild conditions. Protecting the amido hydrogen in the ring is also used during alkylation if necessary as known to the art. Alkyl substituents at the 1 or 3-positions of the indolone ring are introduced by forming the lithio derivatives at the ring position, such as using butyl lithium, followed by reaction with a lower alkyl halide, especially an alkyl iodide. This process is similar to that reported by A. S. Kende et al., Syn. Commun. 12 1 (1982).

The compounds of this invention have utility, as specific dopamine agonists, in the treatment of disorders of the cardiovascular system, especially to treat hypertension, to treat angina pectoris, to treat the symptoms of congestive heart failure or to improve kidney function.

More specifically, the compounds of this invention, especially 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride, have proved to be selective peripheral D_2-agonists. For a discussion of various agonist/antagonist activities in the dopaminergic system, one should refer to J. M. Rooyen, et al., S. Afr. Med. J. 59 329 (1981). or I. Cavero et al., Life Sciences, 31 939, 1059 (1982). Otherwise speaking, the main focus of action is at the presynaptic α-dopaminergic receptors which may also be called "D_2-receptors." Activation of the D_2-receptors on the sympathetic nerve terminals inhibits the release of noradrenaline, thereby, promoting vasodilation, among other beneficial cardiovascular actions.

In the perfused rabbit ear artery test [J. P. Hieble et al., Arch. Pharmacol., 309 217 (1979)], 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride had an EC_{50} of 72 nM. It was active in vivo in the dog in both the cardiovaccelerator nerve and perfused hind limb preparations and did not cause tachyphylaxis in the latter preparation as did its 7-hydroxy congener of the prior art. Intravenous infusion of this species of this invention in the DOCA-salt hypertensive and spontaneously hypertensive rats reduced blood pressure and heart rate. A similar but weaker effect on blood pressure and heart rate was observed with the lead compound in the renal hypertensive rat and in the normotensive rat tests. In conscious DOCA salt hypertensive rats, oral doses of 10 mg/kg of the di-n-propylaminoethyl compound demonstrated an anti-hypertensive effect. This species seems more readily absorbed from the gastrointestinal tract than is its 7-hydroxy congener.

The pharmaceutical compositions of this invention which have pharmacodynamic activity within the cardiovascular system, for example renal vasodilatation, correcting hemodynamic imbalance, anti-anginal activity, hypotensive activity and bradycardia, are prepared in conventional dosage unit forms by incorporating a

compound of formula I, or a pharmaceutically acceptable acid addition salt thereof, into a nontoxic pharmaceutical carrier according to accepted pharmacy procedures in a nontoxic quantity sufficient to produce the desired pharmacodynamic activity in a subject, animal or human. Preferably, the compositions will contain the active ingredient in an active but nontoxic quantity selected from the range of about 50 mg to about 500 mg, preferably about 75–250 mg, of active ingredient, as the base, per dosage unit. This quantity depends on the relative potency of the base compound compared with that of the prototypal species, 4-(2-di-n-propylaminoethyl)-2(3H)-indolone, as well as on the specific biological activity desired, the route of administration, that is, whether oral or parenteral, and the condition and size of the patient.

The pharmaceutical carrier employed for the dosage units is, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate or stearic acid. Exemplary of liquid carriers are isotonic saline for parenteral use or syrup, peanut oil, olive oil or water for soft gelatin capsules. Similarly, the carrier or diluent may include any time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or admixed with a wax. Such sustained release products as well as prodrug derivatives which may be gradually metabolized to the active parent can be employed to prolong the unique biological activity of the compounds of this invention or to attack receptors at a specific location.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier for oral or rectal administration is used, the mixed preparation can be tableted, placed in a hard gelatin capsule in powder or sustained release pellet form, in a suppository or in the form of a troche or lozenge. The amount of solid carrier will vary widely but, preferably, will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampul or an aqueous or nonaqueous liquid suspension for oral administration.

The method of this invention for producing D_2-agonist activity manifests itself by inducing renal vasodilatation, anti-anginal, anti-hypertensive and bradycardic activity. It comprises administering orally, rectally or parenterally to a subject in need of such activity a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, usually combined with a pharmaceutical carrier, in a nontoxic amount sufficient to produce said activity. The route of administration may be any route which effectively transports the active compound to the cardiovascular system receptors which are to be selectively stimulated. Such routes include oral, rectal or parenteral administration, the oral route being preferred. The parenteral administration may be subcutaneous or, preferably, intravenous for critical use.

Advantageously, doses selected from the dosage unit ranges given above will be administered several times, such as from one to five times, a day. The daily dosage regimen is selected from the range of about 50 mg to about 1.0 g, preferably 200–750 mg for oral administration and 50–500 mg for parenteral administration. When the method described above is carried out, D_2-agonist activity is produced.

For an average size human using 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride as an active ingredient, a typical dose to show anti-hypertensive activity would be selected from the range of from about 100–250 mg of base equivalent for each dosage unit which is adapted for oral administration and which is administered orally from 1–4 times daily.

The following examples are designed solely to illustrate the preparation and use of the compounds of this invention. The temperatures are Centigrade. Other variations of these examples will be obvious to those skilled in the art.

EXAMPLE 1

A mixture of 3.44 g (9.63 mmoles) of 4-(2-di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944), 22 cc of dimethylformamide, 1.79 g (9.91 mmoles) of 5-chloro-1-phenyl-1H-tetrazole, 220 cc of acetone, 10 cc of water and 2.90 g (21 mmoles) of anhydrous potassium carbonate was refluxed for about 3 hours at which time thin layer chromatographic analysis (silica gel GF, 75-23-2 ethyl acetate-methanol-conc. ammonium hydroxide) indicated that the reaction was complete.

After cooling the reaction mixture in an ice-bath, the inorganic salts were removed by filtration and washed with acetone. The combined filtrates were concentrated in vacuo. The residual syrup was diluted with saturated brine and extracted with three portions of diethyl ether. The gathered extracts were dried over anhydrous magnesium sulfate, clarified with charcoal and treated with ethereal hydrogen chloride until precipitation was complete. The solid was slurried in diethyl ether and decanted several times, filtered and air-dried to give 3.8 g (86%) of tan 4-(2-di-n-propylaminoethyl)-7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone hydrochloride. Recrystallization from 200 cc of hot acetonitrile gave 2.6 g (59%) of microcrystalline product, m.p. 245°–6°. Evaporation of the mother liquor and recrystallization of the residue from 25 cc of hot acetonitrile gave an additional 400 mg of product, m.p. 244°–5°.

A mixture of 2.64 g (5.78 mmoles) of the phenyl tetrazole ether, 200 cc of glacial acetic acid and 1.49 g of 10% palladium-on-carbon was hydrogenated in a Parr apparatus at 50 p.s.i. for 20 hours at 50°. The warm reaction mixture was filtered through glass fiber filter-paper and the catalyst washed thoroughly with hot glacial acetic acid. The filtrate was concentrated in vacuo, the pale yellow waxy residue distributed in water and ethyl acetate. After acidification of the aqueous phase with 3N hydrochloric acid, the organic phase was separated and extracted once with 1N hydrochloric acid. The combined aqueous phases were adjusted to pH 8.5 with aqueous 10% sodium hydroxide and extracted with a mixture of ethyl acetate and diethyl ether. The combined organic extract was back-washed once with saturated brine, dried over anhydrous magnesium sulfate, clarified with charcoal, treated with ethereal hydrogen chloride and evaporated to dryness in vacuo to give 1.64 g (96%) of pale yellow crystalline solid; 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride. Recrystallization from 260 cc of hot acetonitrile which was concentrated to about 50 cc gave 1.26 g (74%) of pale yellow microcrystalline powder, m.p. 240°–242°.

The hydrochloride salt (500 mg) is shaken in the presence of ether/5% sodium carbonate solution. The ether layer is separated, dried and evaporated to give the free base which is used to prepare other salt forms such as the methanesulfonate, ethanedisulfonate, sulfate

or sulfamate by reacting aliquots of the base in ether with an excess of each acid.

EXAMPLE 2

A mixture of 22.0 g (0.105 mole) of 2-methyl-3-nitrophenylacetic acid (V. Askam et al., J. Chem. Soc. (C) 1969 1935) and 25 cc of thionyl chloride was slowly heated to 75° and the copious evolution of gasses allowed to moderate. The temperature was raised and the solution was refluxed for 1 hour. The reaction was concentrated in vacuo. The residual straw-colored syrup was chased several times with dry toluene, diluted with 100 cc of dry toluene and added to a cool (10°) mixture of 13 g of sodium carbonate in 150 cc of water and 150 cc of toluene containing 14.5 cc (10.6 g, 0.12 mole) of di-n-propylamine with very slow stirring. After 30 minutes, the ice-bath was removed. Stirring was continued for one hour. An additional 0.5 g of solid sodium carbonate was added to the reaction. After 15 minutes, the organic phase was separated, washed with 5% aqueous sodium carbonate followed by 2N hydrochloric acid and, finally water. The organic solution was dried over magnesium sulfate, concentrated in vacuo and pumped free of solvent to give 29.5 g of 2-methyl-3-nitrophenyl-N,N-di-n-propyl acetamide as a straw-colored syrup.

The total syrup (105 mmoles) was taken up in 250 cc of anhydrous tetrahydrofuran and treated with 160 cc of 1.0 M borane in tetrahydrofuran at room temperature for 1 hour. The reaction was refluxed for 2 hours, then cooled. Excess reagent was destroyed by the cautious addition of dry methanol. This solution was concentrated in vacuo. The residual syrup was treated with 40 cc of 6N hydrochloric acid for 1 hour on the steam-bath, cooled, basified with 40% sodium hydroxide and extracted with 3 portions of ether. The combined organic phase was washed once with brine, concentrated in vacuo and distilled in a Kugelrohr apparatus at 115°-118°/0.1 mm Hg to give 21.6 g of a mobile yellow oil; 2-methyl-3-nitrophenylethyl-N,N-di-n-propyl amine.

To a solution of 2.38 g (0.103 gram atoms) of sodium metal in 52 cc of absolute ethanol at room temperature was added 18.51 g (0.07 mole) of the nitro compound in one portion, with stirring, followed by 15.42 g (0.103 mole) of diethyl oxalate. The reaction was refluxed under nitrogen for about 20 minutes, cooled, quenched on 700 cc of ice-water and acidified with 3N hydrochloric acid. This aqueous solution was washed with a small volume of ether, basified to pH 8.5 with solid sodium carbonate and extracted with 3 portions of ether. The combined ether extract was washed with saturated brine, dried over anhydrous magnesium sulfate, clarified with charcoal and concentrated in vacuo. The residue was triturated with cold petroleum ether, filtered and air-dried to give 6.0 g of ethyl 6-(2-di-n-propylaminoethyl)-2-nitrophenylpyruvate as a yellow powder. The triturate was concentrated in vacuo and distilled to give 7.3 g of recovered starting material which was recycled. In the same manner, a total of three recycles provided 11.0 g of ethyl-6-(2-di-n-propylaminoethyl)-2-nitrophenylpyruvate.

A cold (10°) solution of 10.24 g (28.1 mmoles) of the pyruvate in 196 cc of 2% sodium hydroxide was treated with 5.0 cc of 30% hydrogen peroxide dropwise over several minutes. The cooling bath was removed and stirring was continued for 1.5 hours during which time the reaction became much lighter in color. A small amount of insoluble material was removed by filtration. The pH was adjusted to 1.5 by the cautious addition (foaming) of about 12 cc of conc. hydrochloric acid. This solution was concentrated in vacuo at 45°, reconstituted with water and evaporated twice more. The residue was slurried in a minimum volume of dilute hydrochloric acid, filtered and air-dried to give 6.40 g of 2-nitro-6(2-di-n-propylaminoethyl)-phenyl acetic acid hydrochloride as a white powder.

A mixture of 5.83 g (16.9 mmoles) of 2-nitro-6-(2-di-n-propylaminoethyl)-phenyl acetic acid hydrochloride and 0.6 g of 5% palladium-on-carbon in 250 cc of ethanol was hydrogenated at 50 p.s.i. over 5.5 hours. The catalyst was filtered, washed with ethanol, and the filtrate evaporated to dryness in vacuo. The white residue was crystallized from 550 cc of hot acetonitrile to give 3.89 g of 4-(2-di-n-propylaminoethyl)-2(3H)indolone hydrochloride, mp 240°-2°.

Anal. Calcd. for $C_{16}H_{24}N_2O$ HCl: C, 64.74; H, 8.49; N, 9.44. Found: C, 64.82; H, 8.26; N, 9.28.

EXAMPLE 3

A mixture of 2.73 g (10.0 mmoles) of 4-(2-aminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944), 200 cc of dimethylformamide, 1.86 g (10.3 mmoles) of 5-chloro-1-phenyl-1H-tetrazole, 10 cc of water and 2.9 g (21 mmoles) of anhydrous potassium carbonate is stirred at room temperature for 2 days or until thin layer analysis indicates that no starting material remains. The reaction is filtered and the filtrate is acidified with dil. hydrochloric acid, concentrated in vacuo and the residue triturated with abs. ethanol. The triturate is clarified with charcoal and evaporated to dryness in vacuo. The hydrochloride salt of 4-(2-aminoethyl)-7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone is hydrogenated directly in 200 cc of glacial acetic acid using 50% by substrate weight of 10% palladium-on-carbon at 50 p.s.i. for 20 hours at 50°. The warm reaction mixture is filtered. The catalyst is washed thoroughly with hot acetic acid. After the filtrate is concentrated in vacuo, the residue is stripped several times from dilute hydrochloric acid and crystallized from ethanol to give 4-(2-aminoethyl)-2(3H)-indolone hydrochloride.

EXAMPLE 4

A mixture of 0.5 g of 4-(2-aminoethyl)-2(3H)-indolone hydrochloride, prepared as in Example 3, 2.2 g of isobutyraldehyde, 0.3 g of 5% palladium-on-charcoal and 75 ml of glacial acetic acid is hydrogenated at 55 p.s.i. of hydrogen for 5 hours. The catalyst is separated by filtration and washed with acetic acid. The combined mother liquor-washings is evaporated in vacuo to give a residue which is taken up in cold methanol and treated with methanolic hydrogen bromide to give, upon concentration and cooling; 4-(2-di-isobutylaminoethyl)-2(3H)-indolone hydrobromide.

EXAMPLE 5

A mixture of 0.9 g of 4-(2-aminoethyl)-2(3H)-indolone, 0.23 g of 4-benzyloxyphenylacetaldehyde, 0.25 g of 10% palladium-on-charcoal and 100 ml of ethanol is hydrogenated at 50 p.s.i. at 50° until the uptake of hydrogen is complete. After filtration, the mother liquors are evaporated to give 4-[2(4-hydroxyphenethylamino)-ethyl]-2(3H)-indolone as the residue. This base in alcohol is treated with an excess of methylsulfonic acid to give the methylsulfonate salt.

Repeating this reaction with 4-n-propylaminoethyl-7-hydroxy-2(3H)-indolone and butyraldehyde gives 4-n-butyl-n-propylamino-ethyl-7-hydroxy-2(3H)-indolone hydrochloride.

EXAMPLE 6

Substituting 2.2 g of 4-(3-dimethylaminopropyl)-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944) for 4-(2-di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide in Example 1 gives 4-(3-dimethylaminopropyl)-7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone hydrochloride and, then, 4-(3-dimethylaminopropyl)-2(3H)-indolone base as well as the ethanedisulfonate salt as described above.

Substituting 4-n-propylaminoethyl-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944) gives 4-n-propylaminoethyl-2-(3H)-indolone hydrochloride.

Substituting 4-dimethylaminopropyl-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944) gives 4-dimethylaminopropyl-2(3H)-indolone hydrochloride.

EXAMPLE 7

4-Aminoethyl-2(3H)-indolone (10 g) is reacted with two mole equivalents of allyl bromide and 4 equivalents of triethylamine in acetonitrile with mild heat for several hours. The reaction mixture is evaporated. The residue is suspended in water. The mixture is extracted with ethyl acetate. The extracts are washed, dried and evaporated to give 4-di-allylaminoethyl-2(3H)-indolone. This material (1 g) is dissolved in ether-ethanol and treated with methane sulfonic acid to give the methane sulfonate salt. Using benzyl bromide gives 4-dibenzylaminoethyl-2(3H)-indolone.

EXAMPLE 8

Anhydrous tetrahydrofuran (10 cc) at 20° under nitrogen was treated with 2.0 cc (4.8 mm) of 2.4 M n-butyl lithium in hexane followed by 0.49 g (1.5 mm) of 4-di-n-propylaminoethyl-7-methoxy-2(3H)-indolone hydrochloride and 0.349 g (3 mm) of N,N,N',N'-tetramethylethylene diamine. Gas evolution and dissolution of the salt was observed.

The reaction mixture was cooled in a dry ice-propanol bath and treated with 1.5 mm of iodomethane in one portion. After stirring in the cold for 10 minutes, the bath was removed and stirring continued for 2 hours. The mixture was quenched in 20 cc of saturated ammonium chloride solution, diluted with ethyl ether. The organic layer was separated. The remaining material was again extracted twice. The combined dried extracts were concentrated in vacuo, stripped from ethyl ether and carbon tetrachloride.

Analysis of the solid demonstrated a mixture of 10% starting material and a 50—50 mixture of di- and mono 3-methylated product. The mixture was realkylated to give 169 mg of 3,3-dimethyl-4-di-n-propylaminoethyl-7-methoxy-2(3H)-indolone.

This material is hydrolyzed as described in U.S. Pat. No. 4,314,944, Example 4 then, dehydroxylated in the form of the crude product as described above to give 3,3-dimethyl-4-di-n-propylaminoethyl-2(3H)-indolone hydrochloride.

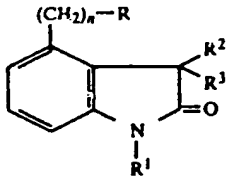
The Kende process was repeated using the same quantities but using 0.61 cc (9.8 mm) of methyl iodide at −70°. The mixture was allowed to warm to −25° and held there for 1 hour followed by 3 hours at room temperature. After working up as described, 4-di-n-propylaminoethyl-7-methoxy-3-methyl-2(3H)-indolone was recovered. This is treated with boron tribromide and, then, 5-chloro-1-phenyl-1H-tetrazole to give 4-di-n-propylaminoethyl-3-methyl-2(3H)-indolone hydrochloride.

EXAMPLE 9

4-(2-di-n-Propylaminoethyl)-2(3H)-indolone hydrochloride (125 mg) is mixed with 200 mg of lactose and 2 mg of magnesium stearate, filled into a hard gelatin capsule and administered to a hypertensive patient from 1-3 times daily.

What is claimed is:

1. A compound of the structural formula:



in which:

R is amino, C_{1-6}-lower alkylamino, di-(C_{1-6}-lower alkyl)amino, allylamino, diallylamino, N-(C_{1-6}-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethyl amino or di-(4-hydroxyphenethyl)amino, and

R^1, R^2 and R^3 are, each, hydrogen or C_{1-4}-lower alkyl; or a pharmaceutically acceptable, acid addition salt thereof.

2. The compound of claim 1 in which R^1, R^2 and R^3 are hydrogen, n is 2 and R is amino, di-n-propylamino, n-propyl-n-butylamino or 4-hydroxyphenethylamino.

3. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

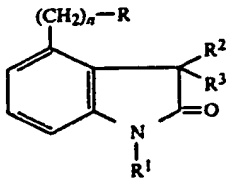
4. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone as the free base.

5. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride.

6. The compound of claim 1 being 4-(2-aminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

7. The compound of claim 1 being 4-(4-hydroxyphenethylaminoethyl-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

8. A pharmaceutical composition having D_2 receptor agonist activity comprising a nontoxic, agonist quantity of a compound of the structural formula:



in which:

R is amino, C_{1-6}-lower alkylamino, di-(C_{1-6}-lower alkyl)amino, allylamino, diallylamino, N-(C_{1-6}-lower alkyl)-N-allylamino, benzylamino, bibenzylamino, phenethylamino, diphenethylamino, 4-

hydroxyphenethylamino or di-(4-hydroxyphenethyl)amino, and

R^1, R^2 and R^3 are each hydrogen or C_{1-4}-lower alkyl; or a pharmaceutically acceptable acid addition salt thereof, in dosage unit form, combined with a pharmaceutical carrier.

9. The composition of claim 8 in which the D_2-agonist compound is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

10. The composition of claim 8 in which the D_2-agonist compound is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride.

11. The composition of claim 8 in dosage unit form adapted for use as an antihypertensive composition.

12. The composition of claim 8 in which the quantity per dosage unit is selected from the range of 50–500 mg base weight of said compound.

* * * * *

ATTACHMENT E

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,452,808

DATED : June 5, 1984

INVENTOR(S) : Gregory Gallagher, Jr.

It is certified that error appears in the above—identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 1 at column 10 line 25 of the patent, after "in which:" and before "R is ..." insert -- n is 1-3, -- .

In claim 8 at column 10 line 64 of the patent, after "in which:" and before "R is ..." insert -- n is 1-3, -- .

Signed and Sealed this

First Day of October 1985

Attest:

Ruth C. Mason

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks—Designate

ATTACHMENT H

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

4087

WILLIAM H. EDGERTON
P. O. BOX 7929
PHILADELPHIA, PA 19101

DATE MAILED
10/09/87

029605

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,452,808	173	450	----	06/447,564	06/05/84	12/07/82	04	NO	PAID
2	4,454,065	173	450	----	06/507,326	06/12/84	06/23/83	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	SKB 14136
2	SKB 14120-C1

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PTO-436 (REV. 1-86)

ATTACHMENT F

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER 001181

75N4/0929
SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-U.S.
UW2220
P.O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

14136 4Q95

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,452,808	185	2900	----	06/447,564	06/05/84	12/07/82	12	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	SKB 14136

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ATTACHMENT G

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
001181

SMITHKLINE BECKMAN CORPORATION
CORPORATE PATENTS - U.S., UW2220
P.O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

DATE MAILED
09/24/91

167045

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,440,775	171	495	----	06/389,837	04/03/84	06/18/82	08	NO	PAID
2	4,440,939	174	1670	----	06/439,088	04/03/84	11/04/82	08	NO	PAID
3	4,443,375	174	1670	----	06/436,894	04/17/84	10/26/82	08	NO	PAID
4	4,452,808	174	1670	----	06/447,564	06/05/84	12/07/82	08	NO	PAID
5	4,738,969	173	830	----	06/876,135	04/19/88	06/19/86	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
	11410
1	~~RICASE6901V2~~
2	SKB 14076-2
3	WELLWYN1173
4	SKB 1413
5	WELWYN.

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PTOL-439 (REV. 4-88)